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Stereoselective solid-phase synthesis of 3,4-substituted azetidinones as key intermediates for mono- and multicyclic β-lactam antibiotics and enzyme inhibitors

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Abstract—The polymer-supported Staudinger reaction proceeded smoothly under mild conditions to give the corresponding β-lactams in good to high overall yields with excellent *cis*-selectivity. Upon applying this reaction system, an efficient asymmetric synthesis of β-lactams was accomplished, when chiral acid chlorides or chiral aldehydes were used. These optically active β-lactams would be useful precursors for the generation of combinatorial libraries of potential antibiotics and enzyme inhibitors.

The importance of β-lactam derivatives to medicinal chemistry has been clearly demonstrated.[1] Owing to their high efficacy and extremely safe toxicological profile, they are the agents of choice in the current therapeutic index for bacterial infections. Tremendous efforts have been made for the synthesis and structural modification of the β-lactam nucleus to increase antimicrobial activity and pharmacokinetic performance. However the rapid emergence of bacterial strains resistant to most generally used members of this class of compound has stimulated extensive research for novel β-lactams that are stable to β-lactamase and possess high potency and broad spectrum activity both in vitro and in vivo.

Apart from their clinical use, recent reports on the use of β-lactams for purposes other than antibiotics is gaining attention. This four-membered cyclic amide has been extensively used for the synthesis of several biological active heterocyclic compounds: the anti-tumor drug paclitaxel (Taxol™) can be prepared by coupling of naturally occurring baccatin and an appropriately substituted hydroxy β-lactam.[2] Additionally, it has been established that certain β-lactams have cholesterol-lowering properties.[3]

Solid-phase organic synthesis (SPOS)[4] has attracted much attention recently due to its potential for the generation of molecular diversity within the context of combinatorial libraries. These chemical libraries have furnished unprecedented numbers of novel entities, which can be screened for potential biological activities.[5]

Following our interest in the applications of solid-phase methodologies to the synthesis of β-lactam compounds,[6] we report herein the asymmetric solid-phase synthesis of 3,4-substituted β-lactams as key intermediates for the synthesis of biologically interesting mono- and multicyclic β-lactam compounds.

For the generation of the β-lactam ring we have chosen the classical Staudinger reaction[7] using Wang resin as a cost effective solid support. Commercially available Fmoc-glycine tethered to the support **1** was used as starting material and then deprotected by treatment with 30% piperidine in DMF to obtain resin **2** (Scheme 1). The solid-supported amine **2** was then condensed with 3,4-dimethoxybenzaldehyde **3a** (R^1 = 3,4-dimethoxyphenyl) in DMF containing 1% acetic acid according to the efficient methodology developed by Boyd,[8] to give the aldimine **4a**. Subsequent [2+2] cycloaddition with the ketene, obtained in situ from the phenoxyacetyl chloride **5a** (R^2 = PhO) and Et_3N, afforded the desired resin bound β-lactam **6aa**. This reaction sequence was monitored using FT-IR spectroscopy and ^{13}C gel-phase NMR spectroscopy.[9]

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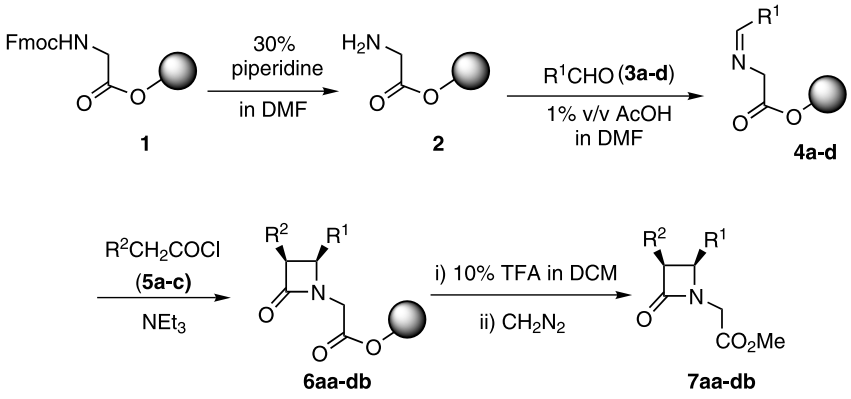
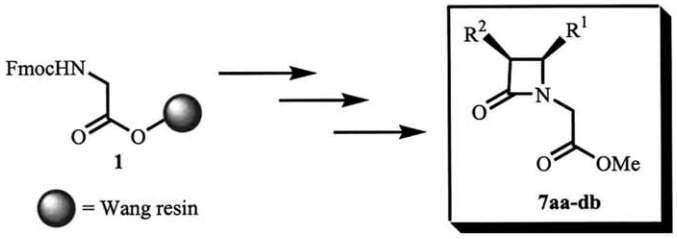
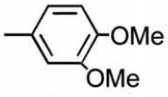
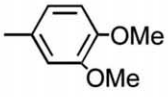
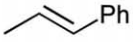
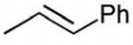
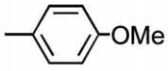
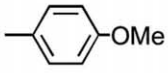
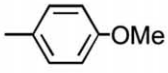


Scheme 1.

Table 1. Solid-phase synthesis of β-lactams



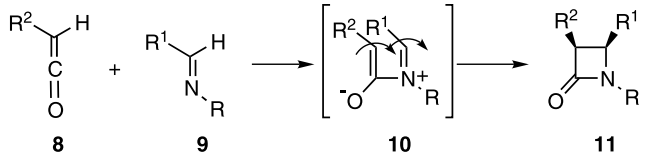
Entry	Comp.	R^1	R^2	Yield[b] (%)
1	**7aa**		PhO	78
2	**7ab**		PhthN[a]	45
3	**7ba**		PhO	51
4	**7bb**		PhthN[a]	44
5	**7ca**		PhO	68
6	**7cb**		PhthN[a]	38
7	**7cc**		MeO	70
8	**7da**		PhO	48
9	**7db**		PhthN[a]	53

[a]Phth=Phthaloyl.
[b]Overall isolated yield after flash chromatography (based on the initial loading level of Fmoc-gly-Wang resin).

The conditions for cleavage of the resin bound β-lactam **6aa** were next examined. While treatment with aluminum chloride[6a] gave 40% overall yield, use of 10% trifluoroacetic acid in dichloromethane was found to be the most effective method for the cleavage, affording the β-lactam **7aa** as its methyl ester in 78% overall isolated yield (based on the manufacturer's loading of the Wang resin).

This solid-phase synthesis and cleavage conditions were applied to the generation of a small library of β-lactam compounds (Table 1). Good to high overall yields of the β-lactams were obtained, with excellent *cis*-selectivity (the *trans* isomers were not detected at all).[10]

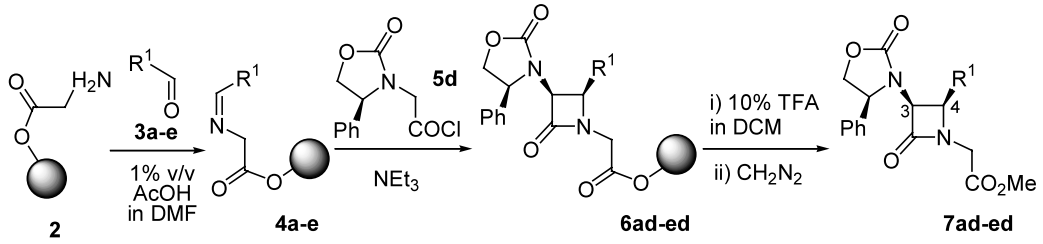
On the basis of these results, we next tried to carry out an asymmetric version of this solid-phase synthesis, in order to develop a useful procedure for the generation of chiral intermediates for the synthesis of biologically interested β-lactams. The chiral glycine derivative **5d**, which has the oxazolidinone moiety as a chiral auxiliary, was prepared according to the literature (Table 2).[11] Next, the asymmetric Staudinger reaction was carried out on the solid support between **5d** and the different resin bound aldimines **4a–e** in the presence of triethylamine. As can be seen from Table 2, optically active β-lactams **7ad–ed** were obtained, after cleaving from the resin, in good to high overall isolated yields with high diastereoselectivity.[12] According to previous studies in solution phase chemistry,[13] the Staudinger reaction takes place in two steps, starting with nucleophilic attack of the nitrogen of the aldimine **9** over the carbonyl of the ketene **8** to form a zwitterionic intermediate **10**, which then undergoes a thermal conrotatory electrocyclization to give the β-lactam product **11** (Scheme 2). The diastereoselectivity is controlled by the difference in thermodynamic stability between the two transition state conformations on the second step. The absence of electrostatic repulsion between the lone pair of the carbonyl oxygen and the phenyl of the oxazolidinone in the transition state that lead to the formation of diastereoisomers **7ad–ed**, explains such stereoselectivity.

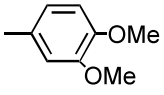
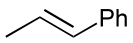
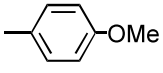
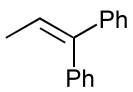


Scheme 2.

This synthetic sequence can be applied to the preparation of enantiomerically pure α-amino acids.[14] Besides, compounds **7bd** and **7ed** are particularly interesting since they have been recently reported as precursors of the novel, highly active, carbacephem antibiotics.[15]

Table 2. Asymmetric solid-phase synthesis of β-lactams using oxazolidinone **5d** as chiral auxiliary



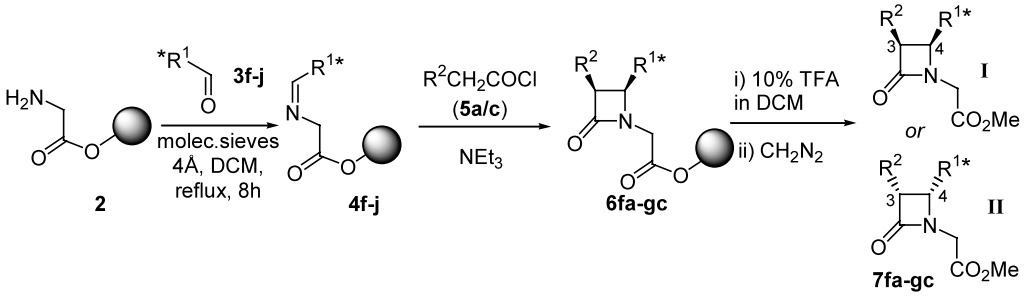
Entry	Compound	R^1	Yield[a] (%)	ds[b]
1	**7ad**		45	> 25/1
2	**7bd**		36	n.d.[c]
3	**7cd**		78	> 25/1
4	**7dd**		46	> 25/1
5	**7ed**		42	8/1

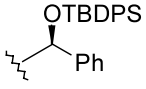
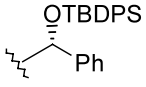
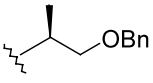
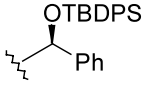
[a]Overall isolated yield after flash chromatography (based on the initial loading level of Fmoc-gly-Wang resin). [b]Determined by ^{1}H NMR from crude material. [c]not determined.

The use of chiral aldehydes for the formation of optically active β-lactams could provide compounds with functionalities at C(4), which are versatile intermediates for the syntheses of novel forms of important carbacephems, isooxacephems and other multicyclic β-lactams.[16] For the solid-phase version of this asymmetric reaction we treated resin bound glycine **2** with (*S*)-(*tert*-butyldiphenylsilanyloxy)phenylacetaldehyde **3f**, obtained in three steps from (*S*)-methyl mandelate[17] (Table 3, entry 1). In this case, we found that condensation proceeds more easily and under very mild conditions by simply refluxing a suspension of the resin and an excess of the aldehyde in dichloromethane in the presence of 4 Å molecular sieves. Aldimine **4f** was then treated with the ketene derived from phenoxyacetyl chloride **5a**, to give the β-lactam **6fa** which, after cleavage and esterification, led to the product **7fa** in 61% yield (based on the initial loading of resin **1**).

Upon applying these optimized conditions, an efficient asymmetric Staudinger reaction of various resin bound chiral aldimines with achiral acid chlorides was accomplished. The results are summarized in Table 3.[18] Good yields and high diastereoselectivity were obtained in most of the cases. Cossío and co-workers[13] explained the high stereocontrol on the basis of the stabilizing interaction between the C–O(N) σ* orbital and the p atomic orbital of the C(3) atom, in the second transition state of the reaction. The solid-phase cycloaddition using the aldimine derived from (*S*)-3-benzyloxy-2-methylpropanal (entry 5), did not proceed as expected. Chiral β-lactam derivative **7ja** was obtained in 25% yield in a 2/1 inseparable mixture with its diastereoisomer. Interestingly, when (*S*)-3-*tert*-butyldiphenylsilanyloxy-2-methylpropanal was used, the reaction sequence proceeded in very low yield presumably due to premature deprotection of the primary hydroxy group.

Table 3. Asymmetric solid-phase synthesis of β-lactams using chiral aldehydes



Entry	Comp.	R^1	R^2	major diastereo-isomer	Yield[a] (%)	ds[b]
1	**7fa**		PhO	**I**	61	> 25/1
2	**7ga**		PhO	**I**	67	10/1
3	**7ha**		PhO	**II**	70	> 25/1
4	**7ia**		PhO	**I**	65	10/2
5	**7ja**		PhO	**I**	25	2/1
6	**7fc**		MeO	**I**	57	8/1
7	**7gc**		MeO	**I**	41	> 25/1

[a]Overall isolated yield after flash chromatography (based on the initial loading level of Fmoc-gly-Wang resin). [b]Determined by ^{1}H NMR from crude material.

Analogues of mandelate and lactate-derived β-lactams (entries 1–4, 6 and 7) have been reported as key intermediates for the synthesis of renin inhibitors[17] and carbapenem antibiotics,[19] respectively.

In summary, we have described an efficient solid-phase methodology for the asymmetric synthesis of 3,4-substituted β-lactams using the stereocontrolled ketene–imine cycloaddition with cost-effective resin linkers as the solid-support. The present procedure could be quite useful for the synthesis of precursors for various antibiotics and other biologically interesting molecules. The applications of this method to the solid-phase synthesis of novel carbacephem antibiotics is currently in progress.

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7. For Staudinger reaction on solid-phase, see: Ruhland, B.; Bhandari, A.; Gordon E. M.; Gallop, M. A. *J. Am. Chem. Soc*. **1996**, *118*, 253–254.
8. Boyd, E. A.; Chan, W. C.; Loh, V. M., Jr. *Tetrahedron Lett*. **1996**, *37*, 1647–1650.
9. Aldimine **4a**: IR: 1650 cm^{-1} (C=N); ^{13}C gel phase (50 MHz, $CDCl_3$) δ 164.9 (C=N, C=O), 149.2, 144.9 (arom. *O-ipso*), 110.2, 108.8 (arom. *O-ortho*), 55.8 (CH_3O). β-lactam **6aa**: IR: 1772 cm^{-1} (β-lactam); ^{13}C gel phase (50 MHz, $CDCl_3$) δ 165.9 (C=O), 156.7, 148.8, 145.0 (arom. *O-ipso*), 115.3, 110.7 (arom. *O-ortho*), 82.5 (C-3), 62.5 (C-4), 55.7 (CH_3O). ^{13}C gel-phase spectroscopy was performed using a conventional 200 MHz apparatus, adapting the technique developed for solid-phase peptide synthesis, see: (a) Epton, R.; Goddard, P.; Ivin, K. J. *Polymer Comm*. **1980**, *21*, 1367–1371; (b) Giralt, E.; Rizo, J.; Pedroso, E. *Tetrahedron* **1984**, *40*, 4141–4152.
10. The relative configuration between H-3 and H-4 was established from the ^1H NMR spectra. The coupling constants of H-3 and H-4 were found to be 4.5–5.3 Hz, which are the expected values for *cis* stereochemistry. Selected spectroscopic data for representative compound **7aa**: IR (film) 1772 (β-lactam), 1746 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.56 (d, $J=18$ Hz, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.46 (d, $J=18$ Hz, 1H), 5.17 (d, $J=4.5$ Hz, 1H), 5.56 (d, $J=4.5$ Hz, 1H), 6.74–7.15 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.75, 52.36, 55.71, 55.90, 62.54, 82.52, 110.61, 111.23, 115.35, 121.42, 121.95, 124.51, 129.15, 148.81, 149.41, 156.74, 165.99, 168.11. Anal. HRMS calcd for $C_{20}H_{21}NO_6$ (M^+, m/z): 371.1369; found: 371.1370.
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12. The absolute configuration of the optically active β-lactams were determined by comparison of the ^1H NMR data with those of a series of related β-lactams, see Ref. 14. Selected spectroscopic data for representative compound **7cd**: IR (film) 1772 (β-lactam), 1757 (ester) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.56 (d, $J=18$ Hz, 1H), 3.67 (s, 3H), 3.82 (s, 3H), 3.94 (dd, $J=6.4$, 7.6 Hz, 1H), 4.17–4.33 (m, 2H), 4.51 (d, $J=18$ Hz, 1H), 4.55 (d, $J=5$ Hz, 1H), 4.98 (d, $J=5$ Hz, 1H), 6.90–7.40 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.49, 52.17, 55.17, 59.63, 61.66, 64.04, 70.04, 114.23, 124.44, 127.27, 128.94, 129.25, 129.34, 136. 30, 156.66, 159.87, 163.88, 168.17. Anal. calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.63; N, 6.67%.
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17. Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Terashima S. *Tetrahedron Lett*. **1990**, *31*, 3031–3034.
18. Absolute configuration was determined by comparison of the ^{1}H NMR data with those of a series of related β-lactams, see Ref. 19. Selected spectroscopic data for representative compound **7fa**: IR (film) 1774 (β-lactam), 1746 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 9H), 3.76 (s, 3H), 3.97 (d, $J=18$ Hz, 1H), 4.28 (d, $J=18$ Hz, 1H), 5.53 (dd, $J=5.3$, 9.2 Hz, 1H), 5.07 (d, $J=5.3$ Hz, 1H), 5.26 (d, $J=9.2$ Hz, 1H), 6.71–7.63 (m, 20H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.08, 26.90, 42.90, 52.20, 63.59, 80.55, 115.58, 121.85, 127.23, 127.62, 127.73, 127.91, 128.06, 129.09, 129.49, 129.65, 132.66, 133.61, 135.34, 135.80, 139.76, 157.63, 167.56, 168.56. Anal. HRMS (FAB+) calcd for $C_{35}H_{37}NO_5Si$ (M+1, m/z): 580.2519; found: 580.2501.
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